POSTER SESSION

1013 Prognostic Markers

Sunday, March 30, 2003, 9:00 a.m.-11:00 a.m.
McCormick Place, Hall A
Presentation Hour: 10:00 a.m.-11:00 a.m.

1013-68 N-Terminal Brain Natriuretic Peptide: The New Gold Standard in Predicting Mortality in Patients With Advanced Heart Failure

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Background. Selection of patients for cardiac transplantation is difficult and has traditionally relied upon assessing clinical status as well as parameters of LV dysfunction associated with an adverse outcome such as the left ventricular ejection fraction (LVEF), maximum oxygen uptake (VO_2 max) and more recently, composite scoring systems e.g. the heart failure survival score (HFSS). Brain natriuretic peptide (BNP) is well established as an independent predictor of prognosis in mild to moderate chronic heart failure (CHF). However, the prognostic ability of NT-proBNP in advanced heart failure is unknown and no studies have compared NT-proBNP to standard clinical markers used in the selection of patients for transplantation. This study describes the prognostic ability of NT-proBNP and compares it to that of the LVEF, VO_2 max and the HFSS in a cohort of patients referred for cardiac transplantation.
Methods. We prospectively studied 128 consecutive patients with advanced CHF referred for consideration of cardiac transplantation. Blood for NT-proBNP analysis was sampled at recruitment and patients followed up for a mean of 280 days. We report on the primary endpoint of all cause mortality and the secondary one of all cause mortality or urgent cardiac transplantation.
Results. The median N-BNP was 1498pg/ml [inter-quartile range 544-3883]. The only univariate and multivariate predictor of all cause mortality was an NT-proBNP level above the median value (RR=5.0 [1.7-22.4], p=0.002). The univariate predictors of all cause mortality or urgent cardiac transplantation were: a RVEF<median (RR=3), a HFSS<median (RR=3) and serum sodium<median (RR=4.3) and NT-proBNP>median (RR=6). The only independent predictors of all cause mortality or urgent cardiac transplantation were an NT-proBNP value>median (RR=6.9 [2.0-23.7], p=0.002) and a serum sodium concentration<median value (RR=4.4 [1.1-9.7], p=0.04). LVEF, VO_2 and HFSS were not independently predictive of mortality in this study.
Conclusions. A single measurement of NT-proBNP in patients with advanced CHF can help to identify patients at the highest risk of death, and is a better prognostic marker than LVEF, VO_2 or HFSS.

1013-69 Relationship Between Serial Measurements of N-Terminal Pro-Brain Natriuretic Peptide and Ambulatory Cardiac Filling Pressures in Outpatients With Heart Failure

Frieder Braunschweig, Astrid Fahrleitner, Stefano Ghio, Maurizio Mangiavacchi, Parwis Fotuhi, Uta C. Hoppe, Mark Harrison, Cecila Linde, Karolinska Hospital, Stockholm, Sweden

Background: Plasma levels of N-terminal pro brain natriuretic peptide (NT-proBNP) are thought to reflect the hemodynamic state and may be useful in the management of outpatients with chronic heart failure (CHF). We used an implanted hemodynamic monitor (IHM) to study the relationship between serial measurements of plasma NT-proBNP levels and ambulatory cardiac filling pressures.
Methods: 13 pt with CHF (58 ± 10 y; LVEF 24 ± 8%; LVEDD 69 ± 13 mm) with an IHM, (Chronicle®, Medtronic Inc) were included. The ambulatory right ventricular systolic pressure (RVSP) and estimated diastolic pulmonary artery pressure (ePAD) were sampled continuously and expressed as the 24 hour median preceding each blood sample. Three to six blood samples for analysis of plasma NT-proBNP (ELISA, Biomedica, normal range < 250 fmol/ml) were taken in each patient with a minimum interval of two weeks in between. Intra-patient correlations between serial NT-proBNP measurements and the corresponding filling pressures were calculated using a random coefficient model (procedure Mixed in SAS).
Results: NT-proBNP plasma levels were elevated in all cases (range 522-1696 fmol/ml) but varied largely between patients. Accordingly, the individual means of NT-proBNP and hemodynamic parameters were not correlated (r=0.12 and 0.13 for RVSP and ePAD respectively). However, serial measurements in the individual patients yielded significant positive intra-patient correlations between NT-proBNP and RVSP (median r=0.71, p=0.006) and ePAD (median r=0.71, p= 0.001), respectively.
Conclusion: In outpatients with chronic heart failure, serial measurements of NT-proBNP in the same individual correlate significantly with hemodynamic parameters and reflect changes of the hemodynamic state over time, despite a large variation of NT-proBNP plasma levels between patients. This finding supports the hypothesis, that serial measurements of NT-proBNP may be a useful tool for outpatient management in chronic heart failure.

1013-70 Neurohumoral Changes as Markers of Progressive Left Ventricular Remodeling in Systolic Heart Failure: Results of the Neurohumoral Substudy of the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD)

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Background: Various neurohormones (NH) are reported as useful diagnostic markers of heart failure (HF) and have been shown previously to correlate with baseline left ventricular ejection fraction (LVEF) and volumes. However, the relationships between temporal changes in these NH and progressive cardiac remodeling in chronic HF have not been studied.
Methods: We evaluated 677 subjects with baseline LVEF 28±10% (mean±SD) enrolled in RESOLVD, a 2-phase 3x2 factorial randomized study of the efficacy of candersartan at various doses and metoprolol in addition to enalapril in systolic HF. Serial changes in LVEF (1.8±6.9%), end-diastolic volume (EDV 18±60ml), and end-systolic volume (ESV 9±53ml) measured by radionuclide ventriculography between baseline and end of phase II (week 42) were correlated with time correspondent changes in brain natriuretic peptide (BNP), N-terminal proatrial natriuretic peptide (Nt-ANP), angiotensin II, aldosterone, endothelin I, norepinephrine and epinephrine.
Results: Among all measured NH, only changes in BNP and Nt-ANP were significantly correlated with changes in EDV, ESV and LVEF consistently irrespective of study phase and therapy as summarized below:

Pearson Coefficients for Changes Between End of Phase II (week 42) and Baseline

Pearson Coefficients: All subjects (N=677) *P = 0.01 **P < 0.0001	Changes in ESV	Changes in EDV	Changes in LVEF
BNP changes	+ 0.24 **	+ 0.24 **	- 0.18 **
Nt-ANP Changes	+ 0.25 **	+ 0.23 **	- 0.10 *
Angiotensin II Changes	- 0.03	- 0.04	+ 0.01
Aldosterone Changes	+ 0.03	+ 0.06	- 0.07
Endothelin I Changes	- 0.03	- 0.03	0.00
Norepinephrine Changes	+ 0.02	+ 0.04	- 0.03
Epinephrine Changes	- 0.02	- 0.03	- 0.02

Conclusions: In this short-term study, serial increases in BNP and Nt-ANP levels predicted ongoing adverse LV remodeling evidenced by declining LVEF, increasing EDV and ESV. Serial measurements of these NH may serve as useful clinical markers for high risk HF patients in whom more aggressive therapy may be warranted.

1013-71 Plasma Norepinephrine Predicts 12-Year Survival in Patients With Reduced Ejection Fractions From the Studies of Left Ventricular Dysfunction (SOLVD)

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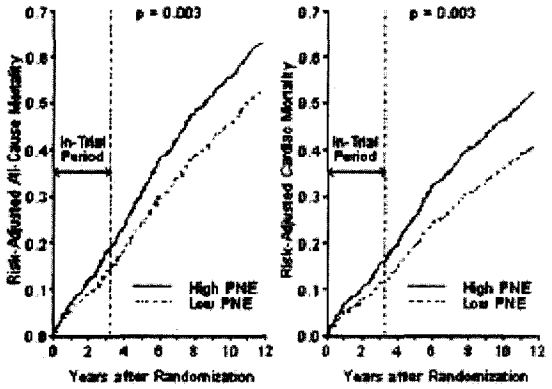
Background: In the Studies Of Left Ventricular Dysfunction (SOLVD), plasma norepinephrine (PNE) was shown to predict in-trial survival among patients with reduced ejection fractions. We examined whether PNE and other neurohormones would also predict long-term survival during a post-trial follow-up of SOLVD.
Methods: PNE (n = 730), plasma renin activity (n = 731), atrial natriuretic peptide (n = 366), and arginine vasopressin (n = 364) were measured at baseline in subsets of 6797 patients previously enrolled in SOLVD. Risk-adjusted survival at 12 years after trial enrollment was compared between patients whose neurohormonal levels lied above and below the group median values.
Results: PNE was the strongest neurohormonal predictor of 12-year survival. After adjusting for age, sex, ejection fraction, cause of heart failure, functional class, treatment and trial assignments, PNE levels above the median of 409 pg/ml were associated with a 36% relative hazard increase in all-cause mortality (95% CI 11 to 66%, p = 0.003) and a 42% relative hazard increase in cardiac mortality (95% CI 13 to 79%, p = 0.003), as compared with levels below the median (Figures). Increases in the levels of the other neurohormones were not predictive of all-cause mortality in the long term.
Conclusion: Elevated PNE remains a powerful and independent predictor of increased

12-year all-cause and cardiac mortalities in patients with left ventricular systolic dysfunction, including those without overt heart failure at baseline.



1013-72 **Limited Diagnostic Accuracy of B-Type Natriuretic Peptide to Predict Cardiac Filling Pressures in Patients Treated for Severe Congestive Heart Failure**

William A. Parsonage, Julia Potter, Gus Koerbin, Andrew J. Galbraith, The Prince Charles Hospital, Brisbane, Australia

Background: Measurement of plasma B- type natriuretic peptide (BNP) is a novel and accurate non-invasive method of diagnosing congestive heart failure (CHF) in patients presenting with dyspnoea. In view of the relationship between BNP and elevated cardiac filling pressures it has been suggested that BNP may be used to guide therapy in patients with established CHF. However the accuracy of BNP for predicting filling pressures in patients receiving conventional medical treatment for severe CHF has not been well documented. We studied this relationship in a large cohort of patients.
Method: We sampled blood for measurement of BNP in 76 patients with severe CHF immediately prior to right heart catheterisation. Plasma BNP was measured using the commercially available Triage BNP® fluorescent immunoassay (Biosite Diagnostics, Velozy, France). Diagnostic accuracy and the predictive value of BNP for a pulmonary capillary wedge pressure (PCWP) of >15mmHg was calculated in the usual way to determine the most accurate cut off value for BNP.
Results: Patients had severe CHF indicated by a mean PCWP of 20±12mmHg and cardiac index of 2.4±0.7l/min/m^2, despite the fact that >80% were on treatment inhibiting the renin-angiotensin system and 36% were taking a beta blocker. A BNP of >100pg/ml gave a sensitivity of 56% and a specificity of 91% for PCWP >15mmHg. The negative predictive value of this level for a PCWP>15mmHg was 64% and the diagnostic accuracy 72%.
Conclusion: This is the largest study validating a commercially available BNP assay against invasively measured hemodynamics in a cohort of patients with severe CHF despite conventional treatment. In this cohort the diagnostic accuracy of BNP for prognostically important elevation of PCWP is limited. Relying on BNP alone to guide therapy would lead to underestimation of PCWP in over a third of patients. It is possible that the relationship between PCWP and BNP is confounded by conventional CHF treatment or that the relationship simply breaks down at the severe extreme of the disease spectrum. Our results suggest that there may be limitations to the use of BNP guided therapy in patients with CHF.

1013-73 **Elevated Troponin I Predicts Clinical Events in Patients Admitted With Acute Heart Failure: Insights From the RITZ-4 Trial**

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Background: Cardiac troponins (cTn) are important prognostic indicators in patients with acute coronary syndrome (ACS) and may be useful for risk stratifying patients with heart failure (HF). Few data are available to describe patients with ACS in the setting of acute HF. The relationship of cTn to clinical outcomes has not been described in this patient population. The purpose of this analysis was to characterize the relationship of cTn I and clinical outcomes among patients with acute ischemic HF enrolled into the RITZ-4 study.
Methods: RITZ-4 was a multi-center, randomized, double-blind, placebo controlled trial of the endothelin receptor antagonist tezosentan in patients admitted with ACS and acute HF. 193 patients were enrolled in this study. ACS was defined by ECG changes, or CK, CKMB, cTn T, or cTn I. The primary endpoint of RITZ-4 was the combined incidence of death, worsening HF, or recurrent or new ischemia or MI, within 72 hours after randomization. Patients with baseline cTn I values were included in this analysis. Results: 133 patients had values for cTn I at admission in RITZ-4 and were included in this analysis. The median (25^{th}, 75^{th}) age of this population was 68.5 (56, 76) years. The population was 51% men, and 72% were caucasian. Forty-two patients had cTn I < 1.0 ng/mL and 91 patients had cTn I ≥ 1.0 ng/mL. Patients with cTn I ≥ 1.0 ng/mL had a higher incidence of the composite primary endpoint as compared to patients with cTn I < 1.0 ng/mL, 28.6% vs 23.8%, respectively, odds ratio 1.15, 95% CI 1.01-1.32, p=0.04.
Conclusions:
The data from this retrospective analysis of RITZ-4 suggest that an elevated cTn I on admission in patients with acute ischemic HF is associated with a higher short-term risk of death, worsening heart failure, or recurrent or new ischemia or MI. These results suggest that ischemia and myocyte necrosis is important prognostically in the setting of acute HF and is likely a significant contributor to worse outcomes. cTn may be a useful prognostic marker or risk stratification tool in future clinical HF trials and potentially clinical practice, particularly in patients with underlying ischemic heart disease.

1013-74 **Predictors of Mortality After Hospitalization for Decompensated Heart Failure**

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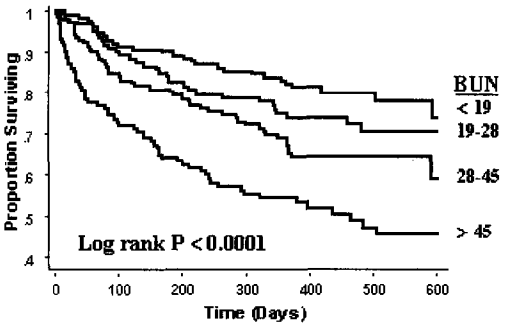
Background: Hospitalization for decompensated heart failure (HF) is associated with a high mortality after discharge. Despite the large number of hospital admissions for HF, little data are available on the outcome of such patients after hospital discharge.
Methods: The effect of baseline clinical parameters on mortality was evaluated in 560 patients (mean age 63 ± 14 years, 377 male) with a previous diagnosis of HF (96% with NYHA class III or IV) who were admitted for decompensated HF.
Results: During a mean follow-up of 343 ± 185 days, 177 patients (32%) died. A Cox proportional-hazards model, adjusted for age, gender, diabetes, primary etiology of HF stratified as ischemic or nonischemic, sodium, blood urea nitrogen (BUN), creatinine, and medical therapy (ACE inhibitors, β-blockers, digoxin, and amiodarone) identified the following variables as predictors of increased mortality: age > 65y (RR = 1.5, 95% CI 1.1-2.1, p = 0.01), ischemic HF (RR = 1.8, 95% CI 1.3-2.6, p = 0.001), sodium ≤ 135 (RR = 1.8, 95% CI 1.3-2.5, p = 0.004) and elevated BUN. The risk of death increased continuously with each quartile of BUN (Figure), with a 3-fold increase in mortality in patients in the upper compared to the lower quartile of BUN (95% CI 1.7-5.3, p = 0.0003). Creatinine was not a predictor of mortality after adjustment for other covariates.
Conclusion: Simple clinical variables provide useful prognostic information in patients with decompensated HF. BUN appears to be the most powerful predictor of post-discharge outcome.



1013-75 **Uncovering Heart Failure in Patients With Bronchospasm: Rationale for the Early Use of B-Type Natriuretic Peptide in the Emergency Department**

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Introduction: Plasma B-type natriuretic peptide (BNP) determination can be used to reliably identify patients with acute congestive heart failure (CHF) in patients presenting in the emergency department (ED) with acute dyspnea. Impaired left ventricular (LV) systolic and diastolic function as well as increased left ventricular (LV) mass are asssociated with increased circulating BNP levels. Heart failure, asthma, chronic obstructive pulmonary disease (COPD), and other bronchospastic disorders, are syndromes where dyspnea and wheezing are overlapping signs, and hence, these syndromes are often difficult to differentiate.
Methods: The BNP Multinational Study was a seven-center prospective study of 1586 patients presenting to the ED with acute dyspnea and had blinded BNP levels measured with a rapid, point-of-care device on arrival. The reference standard for CHF was adjudicated by two independent cardiologists, also blinded to BNP results, who reviewed all clinical data and standardized CHF scores.
Results: A total of 417 subjects (mean age 62.2 years, 64.4% male) had a history of asthma or COPD without a history of CHF. Of these, 87/417 (20.9%, 95% CI 17.1-25.1%) were found to have CHF as the final adjudicated diagnosis. The ED physicians identified 32/87 (36.8%) as having CHF. The mean BNP values were 587.0 and 108.8 pg/ml for those with and without CHF, p < 0.0001. If BNP would have been added to clinical judgement, at a cutpoint of 100 pg/ml, 83/87 (95.4%) of CHF subjects would have been correctly diagnosed. In the 87 subjects who were found to have CHF, 39.0, 22.2, and 54.8% were taking angiotensin converting enzyme inhibitors (ACEI), beta-blockers (BB), and diuretics on a chronic basis, respectively.
Conclusion: The yield of adding routine BNP testing in patients with a history of asthma